1,3-Dipolar Cycloadditions of alpha-Diazo Ketones Derived from N-Protected (S)-Proline with Aromatic and Cycloaliphatic Thioketones

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Abstract: Enantiomerically pure alpha-oxo diazo compounds derived from (S)-proline were used for 1,3-dipolar cycloaddition with aryl and hetaryl thioketones, as well as with cycloalkanethiones. Whereas the reactions with hetaryl thioketones in boiling THF yield alpha,beta-unsaturated ketones via a cascade of cycloaddition, 1,3-dipolar electrocyclization, and desulfurization, the analogous reactions with thiobenzophenone and cycloalkanethiones result in the formation of 1,3-oxathiole derivatives. In the latter case, the 1,5-dipolar electrocyclization of the intermediate thiocarbonyl ylide is the key step of the reaction sequence. In all cases, the isolated products are optically active, i.e., the multistep processes occur with retention of the stereogenic center incorporated via the use of (S)-proline as the precursor of the diazo compounds.

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1,3-Dipolar Cycloadditions of α-Diazoketones Derived from N-Protected (*S*)-Proline with Aromatic and Cycloaliphatic Thioketones

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Enantiopure α-oxodiazo compounds derived from (*S*)-proline were used for 1,3-dipolar cycloaddition with aryl and hetaryl thioketones as well as with cycloalkanethiones. Whereas the reactions with hetaryl thioketones in boiling THF yield α,β-unsaturated ketones *via* a cascade of cycloaddition, 1,3-dipolar electrocyclization, and desulfurization, the analogous reactions with thiobenzophenone and cycloalkanethiones result in the formation of 1,3-oxathiole derivatives. In the latter case, the 1,5-dipolar electrocyclization of the intermediate thiocarbonyl ylide is the key step of the reaction course. In all cases, the isolated products are optically active, *i.e.*, the multistep processes occur with preservation of the chiral center incorporated *via* the use of (*S*)-proline as precursor of the diazo compounds.

1. Introduction. – In recent decades, reactions of diazoalkanes with thioketones have been studied extensively and both their practical importance as well as mechanistic aspects are of current interest. In general, the reactions occur smoothly, even at low temperature, and the kinetic results obtained with diphenyldiazomethane (CH_2N_2) inspired *Huisgen* to name thioketones as 'superdipolarophiles' [1]. Reactions of thioketones **1** with diazoalkanes are especially important, as the [3+2] cycloadducts formed can be isolated in some instances and subsequently used for the generation of reactive thiocarbonyl ylides [2]. It is well known that α-diazocarbonyl compounds **2** are less reactive and for that reason, their reactions with thioketones must be carried out at enhanced temperature or/and in the presence of a catalyst such as $LiClO_4$ [3][4] or $Rh_2(OAc)_4$ [3][5]. Characteristically, reactions with α-diazocarbonyl compounds **2** occur with spontaneous elimination of N_2 from the initially formed cycloadducts **3**, and the intermediate thiocarbonyl ylides **4** undergo competitive 1,3-dipolar or 1,5-dipolar electrocyclizations [6] (*Scheme 1*). In the first case, the corresponding α-oxo-substituted thiiranes **5** are the products, and in the second case, the formation of 1,3-oxathiols **6** is observed. It is worth mentioning that the intermediate α-oxothiocarbonyl ylides **4** do not undergo head-to-head dimerization to give 1,4-dithianes **7**, which is a typical reaction for 1,1-diaryl-substituted thiocarbonyl ylides.

Scheme 1

Typical α-diazocarbonyl compounds **2** applied in 1,3-dipolar cycloadditions with thioketones are α-diazoketones, -esters, and amides [6]. To the best of our knowledge, no studies on reactions of thioketones with optically active α-oxodiazo compounds have been reported yet.

In organic synthesis, natural α-amino acids offer an extremely useful and easily available pool of chiral substrates. One of the most frequently used examples is (*S*)-proline and its derivatives [7]. However, α-diazoketones of type **8**, derived from N-protected proline, have been explored to a limited extent only. In the first line, they were used as precursors of chiral carbenes/carbenoids generated *in situ* by treatment with metal catalysts such as AgOBz or $Rh_2(OAc)_4$ [8]. In some instances, the carbenoid rearranges to the reactive ketene **9** (*Wolff* rearrangement), which is trapped by nucleophiles to give homoproline derivatives **10** [8c] (*Scheme 2*). On the other hand, the carbenoid attacks the C=O group of the protecting moiety yielding a reactive carbonyl ylide **11**, which subsequently can be trapped by a suitable dipolarophile, *e.g.*, dimethyl acetylene dicarboxylate, to give **12** [8a]. Another important application is the *in situ* generation of reactive sulfur ylides **13** *via* decomposition of **8** in the presence of dimethylsulfide [9]. However, no 1,3-dipolar cycloadditions with N-protected diazo compounds **8** have been reported to date.

Scheme 2

The goal of the present study was to test the reactivity of tioketones towards proline-derived α-diazoketones **8** used as 1,3-dipoles.

2. Results and Discussion. – The starting thioketones **8** with R = Bz, Bn, and Boc are known compounds, which were obtained by treatment of the corresponding N-protected proline chlorides with CH_2N_2 [8a,b][9]. All of them are relatively stable at room temperature, and in solution exist as mixtures of two rotamers as evidenced by NMR spectroscopy.

The first series of experiments was perfomed with thiobenzophenone (**1a**) and the benzoyl derivative **8a** in order to optimize the reaction conditions. Whereas the reaction carried out in toluene at room temperature required 48 h for complete conversion, the analogous experiment in THF was finished after only 21 h. The transformation in THF was slightly accelerated by addition of a catalytic amount (*ca.* 10%) of $LiClO_4$ (15 h). However, heating the mixture of **1a**, **8a**, and $LiClO_4$ in THF at reflux led to vigorous evolution of N_2, and the reaction was already complete after 3 h. The ^{1}H-NMR analysis of the reaction mixture proved the presence of only one product, also existing as a mixture of two rotamers. In all of the experiments, the yield of the isolated product was between 80 and 90%.

The structure of the formed compound **6a** was elucidated based on the spectroscopic data. Thus, the IR spectrum (KBr) showed the presence of only one C=O group (1624 cm^{-1}). In the ^{1}H-NMR spectrum ($CDCl_3$), a characteristic singlet of the major rotamer located at 5.10 ppm is attributed to the =CHS fragment of the 1,3-oxathiole ring [10]. The analogous signal of the minor rotamer appeared at 5.58 ppm. The structure of a 1,3-oxathiole was additionally supported by the ^{13}C-NMR data, and the signals found at 103.4 and 102.8 ppm for the major and minor rotamer, respectively, are of special importance [4][10]. Furthermore, the ESI-MS confirmed the molecular formula $C_{26}H_{23}NO_2S$ (*m/z* 436 for $[M+Na]^+$). The product was optically active and the $[\alpha]_D^{25}$ value in CH_2Cl_2 was –135.4. All these data fit well with the structure of the expected 1,3-oxathiole derivative **6a** (*Scheme 3*). The analogous structures were determined for the products of the reactions of **2a** with the N-benzyl and N-Boc protected diazo compounds **8b** and **8c** in comparable yields.

Scheme 3

In the case of **6a**, the ^{1}H-NMR spectra in (D_6)DMSO were recorded at 22° and 80°. At room temperature, the presence of two rotamers was evidenced by two broad singlets for =CHS at 4.90 and 4.49 ppm, in a ratio of *ca*. 3:2. In addition, two multiplets for H–C(2) of the pyrrolidine ring appeared at 4.15–4.00 and 3.70–3.55 ppm (ratio *ca*. 3:2). In the spectrum measured at 80°, only two broad signals were found at 4.95 and 4.20 ppm.

In a recent publication, reactions of selected bis-hetaryl thioketones with CH_2N_2 leading to 4,4,5,5-tetrahetaryl-1,3-ditiolanes were described [11]. In order to compare the reactivity of hetaryl thioketones containing diverse heteroatoms (O, S, Se) with that of thiobenzophenone (**1a**), the reactions with diazoketones **8** were performed under optimized conditions (THF, $LiClO_4$, reflux). The experiment with bis-(thiophen-2-yl) thioketone (**1b**) and **8a** was complete after 4 h, and again the ^{1}H-NMR analysis revealed the formation of a sole product also existing as a mixture of two rotamers. In contrast to 1,3-oxathioles **6** obtained in the reactions with **1a** (*Scheme 3*), no singlets were detected in the region of 5–6 ppm. Instead, characteristic singlets for H–C(sp^2) appeared at 6.85 and 6.36 ppm for the major and minor rotamer, respectively. After chromatographic workup, the pure product showed in the ^{13}C-NMR spectrum the presence of two C=O groups (196.6 and 169.5 ppm for the major rotamer). In addition, a signal found at 121.7 ppm can be attributed to a CH=C fragment. The ESI-MS with *m/z* 416 ($[M+Na]^+$) confirmed the molecular formula $C_{22}H_{19}NO_2S_2$. This result proves that the formation of the product occurred with loss of a S-atom. Taking these facts in account, we propose that the product formed in the studied reaction corresponds to the structure of the α,β-unsaturated ketone **14a** (*Scheme 4*).

The analogous products were formed in a series of experiments performed with thioketones **1c**–**1e** and diazo compounds **8a** and **8c**. All of them were isolated as oily materials in good yields.

Scheme 4

Among cycloaliphatic thioketones (cycloalkanethiones), adamantanethione (**1f**) and 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**1g**) are favorite models, which are frequently used to study the reactivity of the C=S group [12]. In comparison to other α-oxodiazo compounds [4], the reaction of **1f** with **8a** and **8c** in boiling THF occurred smoothly with evolution of N_2. The chromatographic workup led to only one product in each case, identified as the corresponding 1,3-oxathiols **6d** and **6e**, respectively (*Scheme 5*). It is worth mentioning that in these cases the ^{1}H-NMR spectra in $CDCl_3$ at room temperature showed the presence of a single rotamer. In an analogous manner, the reaction of **8c** with **1g** was complete after 8 h, and the product **6f** was isolated in 41% yield. Unexpectedly, the reaction of **8c** with the structurally related 2,2,4,4-tetramethyl-3-thioxocyclobutanone led to a complex mixture of products. It is worth mentioning that the ^{1}H-NMR spectra recorded in $CDCl_3$ at room temperature showed also the presence of two rotamers of 1,3-oxathioles **6d**, **6e**, and **6f**.

Scheme 5

Finally, the structure of **6f** was established by X-ray crystallography (*Figure*). The compound in the crystal is enantiomerically pure and the absolute configuration of

the molecule has been determined independently by the diffraction experiment. The molecule has the expected proline *S*-configuration.

Figure. *ORTEP plot* [13] *of the molecular structure of* **6f** (with 50% probability ellipsoids; arbitrary numbering of the atoms).

3. Conclusions. – The present study showed that proline-derived α-oxodiazo compounds **8** are useful 1,3-dipoles in reactions with aromatic and cycloaliphatic thioketones **1**. However, the type of the obtained products differs depending on the type of thioketone used. Whereas thiobenzophenone (**1a**) and cycloalkanethiones **1f** and **1g** afford 1,3-oxathioles **6**, the bis-hetaryl thioketones **1b**–**1e** yield α,β-unsaturated ketones **14**. The mechanistic explanation is based on the assumption of the intermediate formation of a reactive thiocarbonyl ylide of type **4** (*Scheme 1*). This type of 1,3-dipoles with an extended π-system is known to undergo preferably electrocyclization reactions, which can occur as 1,3-dipolar or 1,5-dipolar ring closure. In the first case, 2-acylated thiiranes are the expected products. In many instances, however, the spontaneous extrusion of S is observed. Apparently, the hetaryl substituents are vitally important for the 1,3-dipolar electrocyclization and the subsequent elimination of S. The replacement of the hetaryl groups by Ph leads to the alternative 1,5-dipolar electrocyclization of the intermediate thiocarbonyl ylide **4**. In contrast to some other 1,3-oxathiols [4], the products **6** do not undergo isomerization *via* ring opening to form thiiranes in solution.

The application of the enantiopure α-oxodiazo compounds **8** allows the preparation of a series of optically active 1,3-oxathiole derivatives **6**, as well as hetaryl-substituted α,β-unsaturated ketones **14**, which potentially are attractive building blocks for asymmetric syntheses, *e.g.*, as activated dieno- and dipolarophiles.

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Experimental Part

1. *General*. M.p.: *MEL-TEMP. II* (*Aldrich*); uncorrected. Column chromatography (CC): silica gel (70–230 mesh, *Merck*). IR Spectra: *NEXUS FT-IR* instrument; in KBr or as film; absorptions in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR Spectra: *BRUKER AVANCE III* instrument (^{1}H at 600 and ^{13}C at 150 MHz) using solvent signal as reference; in $CDCl_3$; chemical shifts (δ) in ppm; coupling constants J in Hz. The majority of the ^{13}C signals were assigned with the aid of DEPT spectra. ESI-MS: *Varian 500 MS* LC Ion Trap spectrometer. Optical rotation was measured on a *Perkin-Elmer 241 MC* polarimeter at 20º.

2. *Starting Materials.* 1-(*N*-Benzoylpyrrolidin-2-yl)-2-diazoethanone (**8a**), 1-(1-benzylpyrrolidin-2-yl)-2-diazoethanone (**8b**), *tert*-butyl 2-(diazoacetyl)pyrrolidine-1-carboxylate (**8c**), were prepared according to [8b]. Thiobenzophenone (**1a**), the symmetrical heteroaromatic thioketones (**1b**, **1c**, **1d**) and the nonsymmetrical heteroaromatic thioketone (**1e**) were obtained from the corresponding ketones according to known procedures [11]. Adamantanethione (**1f**) and 2,2,4,4-tetramethylcyclobutane-1,3-dione (**1g**) were prepared from the corresponding ketones according to the procedure described in [12]. Other reagents used in the present study were commercially available. Reported yields refer to isolated products.

3. *Reactions of Aromatic and Heteroaromatic Thioketones* **1a–e** *with Diazo Compounds* **8a–c**. – *General Procedure*. To a soln. of **8a–c** (1 mmol) and $LiClO_4$ (10 mol%) in freshly distilled THF (2.5 ml), **1a** (1.2 mmol) dissolved in a small amount of

THF was added portion-wise. The mixture was heated at reflux under an Ar atmosphere, and the progress of the reaction was monitored by TLC. The high-field ^{1}H-NMR spectra registered for the crude products showed that compounds **6** and **14** exist in solution as mixtures of C–N rotamers.

3.1. N-*Benzoyl-2-(2,2-diphenyl-[1,3]oxathiol-5-yl)pyrrolidine* (**6a**). The reaction of **8a** with thiobenzophenone (**1a**) was complete after 3 h. The solvent was evaporated, and the crude product was purified by CC (AcOEt/hexane 1:1). Compound **6a** consisted of a *ca*. 60:40 mixture of both rotamers. Yield: 334 mg (80%). White crystals. M.p. 74.2–77.1° (hexane/Et_2O). $[\alpha]_D$ = –135.4 (*c* = 1; CH_2Cl_2).IR (KBr): 2252*m*, 1624*s* (C=O), 1598*m*, 1575*w*, 1447*m*, 1418*m*, 1072*w*, 724*m*. ^{1}H-NMR ($CDCl_3$; values for the minor rotamer in italics): 2.0–2.11 (*m*, 4H, C*H*$_2$C*H*$_2$); 3.40–3.55 (*m*, 2H, C*H*$_2$N); 4.48, *5.14* (br. *s*, 1H, C*H*N); 5.10, *5.58* (br. *s*, 1H, SC*H*); 7.21–7.57 (*m*, 15 arom. H). ^{13}C-NMR ($CDCl_3$): 22.2 (*C*H$_2$); 30.7 (*C*H$_2$); 46.1 (*C*H$_2$N); 58.0 (*C*HN); 95.3 (S*C*H=); 103.4 (C(2')); 126.4, 128.0, 128.1, 128.4, 129.6, 136.7 (for 15 arom. CH); 143.4, 143.6 (for 3 arom. C); 148.9 (C(5')); 170.5 (C=O). ESI-MS (MeOH): 436 (100, [*M*+Na]$^+$).

3.2. N-*Benzyl-2-(2,2-diphenyl-[1,3]oxathiol-5-yl)pyrrolidine* (**6b**). The reaction of **8b** with **1a** was complete after 3 h. The solvent was evaporated, and the crude product was crystallized from MeOH. Yield of **6b**: 352 mg (86%). Colorless crystals. M.p. 93.4–94.5° (MeOH). $[\alpha]_D$ = –40.8 (*c* = 0.5; CH_2Cl_2).IR (KBr): 2964*m*, 2808*s*, 1656*m*, 1494*s*, 1447*s*, 1328*m*, 1173*m*, 1110*s*, 1081*m*, 1003*s*, 742*s*, 700*s*. ^{1}H-NMR ($CDCl_3$): 1.72–2.05 (*m*, 4H, C*H*$_2$C*H*$_2$); 2.15–2.25 (*m*, 1H, C*H*$_2$N); 2.90–3.05 (*m*, 1H, C*H*$_2$N); 3.21–3.25 (*m*, 1H, C*H*N); 3.61 (*AB*, 2H, $^2J_{AB}$ = 12, PhC*H*$_2$); 5.51 (*s*, 1H, SC*H*); 7.23–7.65 (*m*, 15 arom. H). ^{13}C-NMR ($CDCl_3$): 22.7 (*C*H$_2$); 29.4 (*C*H$_2$); 53.2 (*C*H$_2$N); 58.2 (*C*HN); 62.7 (Ph*C*H$_2$); 94.2 (S*C*H=); 102.8 (C(2')); 126.6, 126.7, 127.9, 128.0

(br.), 128.1, 128.6 (for 15 arom. CH); 139.5, 143.9, 144.3 (3 arom. C); 150.9 (C(5')). ESI-MS (MeOH): 400 (100, $[M+H]^+$).

3.3. N-*Boc-2-(2,2-diphenyl-[1,3]oxathiol-5-yl)pyrrolidine* (**6c**). The reaction of **8c** with **1a** was complete after 3 h. The solvent was evaporated, and the crude product was purified by CC (CH_2Cl_2). Compound **6c** consisted of a 71:29 mixture of two rotamers. Yield of **6c**: 230 mg (56%). Pale yellow oil. $[\alpha]_D = -90.2$ (c = 1; CH_2Cl_2). IR (film): 2975*s*, 1694*s* (C=O), 1447*s*, 1390*s*, 1170*s*, 1110*s*, 994*s*, 917*m*, 878*m*, 753*s*, 698*s*. ^{1}H-NMR ($CDCl_3$; values for the minor rotamer in italics): 1.32 (br. *s*, 9H, *t*Bu); 1.84–1.98 (*m*, 4H, C*H*$_2$C*H*$_2$); 3.44–3.50 (*m*, 2H, C*H*$_2$); 4.45–4.60 (br. *m*, 1H, C*H*N); 5.28, *5.37* (br. *s*, 1H, SC*H*); 7.28–7.53 (*m*, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 23.2 (*C*H$_2$); 28.2 (*Me*$_3$C); 30.4 (*C*H$_2$); 46.1 (*C*H$_2$N); 55.4 (*C*HN); 79.5 (Me$_3$*C*); 93.3 (S*C*H=); 103.1 (C(2')); 126.2, 126.4, 128.0 (for 10 arom. CH); 143.8 (for 2 arom. C); 149.7 (C(5')); 154.1 (C=O). ESI-MS (MeOH): 448 (30, $[M+K]^+$), 432 (100, $[M+Na]^+$), 410 (15, $[M+H]^+$).

3.4. N-*Benzoyl-1-(pyrrolidin-2-yl)-3,3-di(thiophen-2-yl)propenone* (**14a**). The reaction of **8a** with bis(2-thienyl)methanethione (**1b**) was complete after 4 h. The solvent was evaporated, and the crude product was purified by CC (AcOEt/hexane 1:1). Compound **14a** consisted of a 78:22 mixture of two rotamers. Yield of **14a**: 312 mg (80%). Yellow viscous oil. $[\alpha]_D = -46$ (c = 1; CH_2Cl_2). IR (KBr): 2971*w*, 2872*w*, 1688*m* (C=O), 1625*s*, 1575*s*, 1417*s*, 1251*m*, 1216*m*, 1078*m*, 852*m*, 701*s*. ^{1}H-NMR ($CDCl_3$; values for the minor rotamer in italics): 1.82–2.20 (*m*, 4H, C*H*$_2$C*H*$_2$); 3.50–3.82 (*m*, 2H, C*H*$_2$N); 4.35–4.91 (*m*, 1H, C*H*N); 6.85, *6.36* (*s*, 1H, *H*C=); 7.02–7.57 (*m*, 11 arom. H). ^{13}C-NMR ($CDCl_3$): 25.3 (*C*H$_2$); 28.6 (*C*H$_2$); 50.2 (*C*H$_2$N); 65.3 (*C*HN); 121.7 (=*C*H); 126.8, 127.3, 127.6, 127.9, 128.2, 128.5, 130.0, 130.2, 130.4 (for 11 arom. CH);

136.4, 138.1, 141.1, 145.4 (3 arom. C, *C*Ar$_2$); 169.5 (C=O); 196.9 (C=O). ESI-MS (MeOH): 416 (100, [*M*+Na]$^+$).

3.5. N-*Benzoyl-1-(pyrrolidin-2-yl)-3,3-di(selenophen-2-yl)propenone* (**14b**). The reaction of **8a** with di(selenophen-2-yl)methanethione (**1c**) was complete after 1 d. The solvent was evaporated, and the crude product was purified by CC (AcOEt/hexane 1:1). Compound **14b** consisted of a 78:22 mixture of two rotamers. Yield of **14b**: 340 mg (70%). Yellow viscous oil. $[\alpha]_D$ = –36.8 (*c* = 1; CH_2Cl_2). IR (KBr): 2949*w*, 2969*w*, 1684*m* (C=O), 1625*s*, 1575*s*, 1417*s*, 1243*w*, 1075*m*, 1017*w*, 698*s*. ^{1}H-NMR ($CDCl_3$; values for the minor rotamer in italics): 1.81–2.18 (*m*, 4H, C*H*$_2$C*H*$_2$); 3.48–3.78 (*m*, 2H, C*H*$_2$N); 4.38–4.80 (*m*, 1H, C*H*N); 6.76, *6.25* (*s*, 1H, *H*C=); 7.02–8.16 (*m*, 11 arom. H). ^{13}C-NMR ($CDCl_3$): 25.4 (*C*H$_2$); 29.7 (*C*H$_2$); 49.7 (*C*H$_2$N); 65.3 (*C*H); 121.6 (=*C*H); 127.9, 128.4, 129.1, 129.0, 130.4, 132.4, 132.7, 133.9, 134.0 (for 11 arom. CH); 136.6, 144.1, 145.3, 151.7 (3 arom. C, *C*Ar$_2$); 169.4 (C=O), 197.2 (C=O). ESI-MS (MeOH): 510 (100, [*M*$^+$+Na]$^+$).

3.6. N-*Boc-1-(pyrrolidin-2-yl)-3,3-di(thiophen-2-yl)propenone* (**14c**). The reaction of **8c** with bis(2-thienyl)methanethione (**1b**) was complete after 3 h. The solvent was evaporated, and the crude product was purified by CC (AcOEt/hexane 1:1). Compound **14c** consisted of a 78:22 mixture of two rotamers. Yield of **14c**: 264 mg (68%). Yellow viscous oil. $[\alpha]_D$ = –56.2 (*c* = 1; CH_2Cl_2). IR (KBr): 2975*m*, 1694*s* (C=O), 1570*s*, 1394*s*, 1254*w*, 1162*s*, 1119*s*, 706*m*. ^{1}H-NMR ($CDCl_3$; values for the minor rotamer in italics): 1.49 (br. s, 9H, *t*Bu); 1.85–2.16 (*m*, 4H, C*H*$_2$C*H*$_2$); 3.40–3.58 (*m*, 2H, C*H*$_2$N); 4.27–4.49 (*m*, 1H, C*H*N); 6.71, *6.78* (*s*, 1H, *H*C=): 7.04–7.49 (*m*, 6 arom. H). ^{13}C-NMR ($CDCl_3$): 23.6 (*C*H$_2$); 28.4 (*Me*$_3$C); 30.3 (*C*H$_2$); 46.2 (*C*H$_2$N); 65.7 (*C*HN); 80.2 (Me$_3$*C*); 119.9 (=*C*H); 126.7, 127.8, 128.0, 128.5, 130.1, 130.4 (6 arom.

CH); 138.0, 141.4, 145.5 (2 arom. C, *C*Ar$_2$); 154.0 (C=O); 198.2 (C=O). ESI-MS (MeOH): 412 (100, [*M*+Na]$^+$).

3.7. N-*Boc-1-(pyrrolidin-2-yl)-3,3-di(selenophen-2-yl)propenon* (**14d**). The reaction of **8c** with di(selenophen-2-yl)methanethione (**1c**) was complete after 1 d. The solvent was evaporated, and the crude product was purified by CC (AcOEt/hexane 1:1). Compound **14d** consisted of a 62:38 mixture of two rotamers. Yield of **14d**: 430 mg (88%). Yellow viscous oil. $[\alpha]_D = -35.4$ (c = 1; CH_2Cl_2). IR (KBr): 2976*s*, 1698*s* (C=O), 1569*s*, 1397*s*, 1365*s*, 1162*s*, 1120*s*, 1014*m*, 839*m*, 736*s*, 696*s*. ^{1}H-NMR ($CDCl_3$; values for the minor rotamer in italics): 1.39 (br. *s*, 9H, *t*Bu); 1.85–2.18 (*m*, 4H, C*H*$_2$C*H*$_2$); 3.42–3.59 (*m*, 2H, C*H*$_2$N); 4.28–4.50 (*m*, 1H, C*H*N); 6.60, *6.68* (*s*, 1H, *H*C=); 7.28–7.44 (*m*, 4 arom. CH); 8.00–8.22 (*m*, 2 arom. CH). ^{13}C-NMR ($CDCl_3$): 23.6 (*C*H$_2$); 28.4 (*Me*$_3$C); 30.6 (*C*H$_2$); 46.8 (*C*H$_2$N); 65.7 (*C*HN); 80.0 (Me$_3$*C*); 119.9 (=*C*H); 128.9, 130.3, 132.2, 133.1, 133.8, 134.5 (6 arom. CH); 143.7, 145.6, 151.8 (2 arom. C, *C*Ar$_2$); 153.9 (C=O); 198.3 (C=O). ESI-MS (MeOH): 506 (100, [*M*+Na]$^+$). Anal. calc. for $C_{20}H_{23}NO_3Se_2$ (483.32): C 49.70, H 4.80, N 2.90; found: C 49.76 H 5.03 N 2.71.

3.8. N-*Boc-1-(pyrrolidin-2-yl)-3,3-di(furan-2-yl)propenone* (**14e**). The reaction of **8c** with bis(2-furyl)methanethione (**1d**) was complete after 3 d. The solvent was evaporated, and the crude product was purified by CC (AcOEt/hexane 1:1). Compound **14e** consisted of a 70:30 mixture of two rotamers. Yield of **14e**: 146 mg (40%). Yellow viscous oil. $[\alpha]_D = -23$ (c = 1; CH_2Cl_2). IR (KBr): 2977*s*, 1689*s* (C=O), 1542*s*, 1404*s*, 1258*w*, 1162*s*, 1121*s*, 1020*m*, 924*w*, 885*w*, 747*m*. ^{1}H-NMR ($CDCl_3$; values for the minor rotamer in italics): 1.38 (br. *s*, 9H, *t*Bu); 1.86–2.20 (*m*, 4H, C*H*$_2$C*H*$_2$); 3.41–3.58 (*m*, 2H, C*H*$_2$N); 4.32–4.52 (*m*, 1H, C*H*N); 6.49–6.90 (*m*, 6 arom. CH); 7.49, *7.51* (br. *s*, 1H, *H*C=). ^{13}C-NMR ($CDCl_3$): 23.6 (*C*H$_2$); 27.6 (*Me*$_3$C); 31.0 (*C*H$_2$); 47.0 (*C*H$_2$N); 66.0 (*C*HN); 80.0 (Me$_3$*C*); 111.2, 112.3, 114.3, 115.6, 118.1, 118.4, 144.5 (6 arom. CH,

=*C*H); 131.0, 146.7, 148.2 (2 arom. C, *C*Ar$_2$); 154.1 (C=O); 198.4 (C=O). ESI-MS (MeOH): 396 (27, [*M*+K]$^+$), 380 (100, [*M*+Na]$^+$).

3.9. N-*Boc-1-(pyrrolidin-2-yl)-3-phenyl-3-(thiophen-2-yl)propenone* (**14f**). The reaction of **8c** with phenyl(2-thienyl)methanethione (**1e**) was complete after 1 d. The solvent was evaporated, and the crude product was purified by CC (AcOEt/petroleum ether 2:3). Compound **14f** consisted of a 63:37 mixture of two rotamers. Yield of **14f**: 278 mg (73%). Yellow oil. $[\alpha]_D = -48$ (*c* = 1; CH_2Cl_2). IR (KBr): 2976*m*, 1690*s* (C=O), 1570*s*, 1478*m*, 1492*m*, 1396*s*, 1265*m*, 1162*m*, 735*m*, 700*m*. ^{1}H-NMR ($CDCl_3$; values for the minor rotamer in italics): 1.42 (br. *s*, 9H, *t*Bu); 1.82–2.06 (*m*, 4H, C*H*$_2$C*H*$_2$); 3.37–3.52 (*m*, 2H, C*H*$_2$N); 4.18–4.43 (*m*, 1H, C*H*N); 6.75, *6.81* (br. *s*, 1H, *H*C=); 6.89–7.42 (*m*, 8 arom. CH). ^{13}C-NMR ($CDCl_3$): 23.5 (*C*H$_2$); 28.4 (*Me*$_3$C); 30.4 (*C*H$_2$); 46.7 (*C*H$_2$N); 65.4 (*C*HN); 79.9 (Me$_3$*C*); 118.4 (=*C*H); 128.0, 128.5, 128.6, 128.7, 128.9, 130.8 (for 8 arom. CH); 138.1, 145.5, 149.3 (2 arom. C, *C*(Ph)Ar); 154.0 (C=O), 198.2 (C=O). ESI-MS (MeOH): 422 (27, [*M*+K]$^+$) 406 (100, [*M*+Na]$^+$) 384(15, *M*+H]$^+$). Anal. calc. for $C_{22}H_{25}NO_3S$ (383.50): C 68.90, H 6.57, N 3.65, S 8.36; found: C 68.23, H 6.77, N 3.58, S 7.99.

4. *Reactions of Cycloalkanethiones* **1f** and **1g** *with Diazo Compounds* **8a** and **8c**. – *General Procedure*. To a soln. of **8a** or **8c** (1 mmol) and $LiClO_4$ (10 mol%) in freshly distilled THF (2.5 ml) was added in portions **1f** and **1g** (1.05 mmol). The mixture was heated at reflux under Ar, and the progress of the reaction was monitored by TLC. The high-field NMR spectrum showed that compounds **6d-f** consisted of a mixture of C–N rotamers.

4.1. N-*Benzoyl-5'-(pyrrolidin-1-yl)spiro[adamantane-2,2'-[1,3]oxathiole]* (**6d**). The reaction of **8a** with adamantanethione (**1f**) was complete after 4 d. The solvent was evaporated, and the crude product was purified by CC (AcOEt/hexane 1:1). Compound

6d consisted of a 53:47 mixture of two rotamers. Yield of **6d**: 140 mg (37%). Yellow viscous oil. $[\alpha]_D = -68.6$ (c = 1; CH_2Cl_2). IR (KBr): 2907*s*, 2854*s*, 1633*s* (C=O), 1578*m*, 1448*s*, 1401*s*, 1100*m*, 1061*m*, 1000*m*, 725*m*, 699*m*. ^{1}H-NMR ($CDCl_3$; values for the minor rotamer in italics): 1.59–1.82 (*m*, 10H, 5 C*H*$_2$); 2.00–2.43 (*m*, 8H, C*H*$_2$C*H*$_2$, 4 C*H*); 3.43, 3.57, *3.69*, *3.79* (br. *s*, 2H, C*H*$_2$N); 4.38, *4.98* (br. *s*, 1H, C*H*N); 4.91, *5.40* (br. *s*, 1H, SC*H*); 7.38–7.49 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 22.3 (*C*H$_2$); 26.3, 26.5 (2 *C*H); 31.1 (*C*H$_2$); 33.8, 35.4, 37.3 (2:1:1, 4 *C*H$_2$); 39.4 (2 *C*H); 46.1 (*C*H$_2$N); 58.0 (*C*HN); 93.7 (S*C*H=); 107.4 (C(2')); 126.8, 127.1, 129.7 (for 5 arom. CH); 137.0 (1 arom. C); 149.3 (C(5')); 170.5 (C=O). ESI-MS (MeOH): 420 (100, $[M+K]^+$).

4.2. N-*Boc-5'-(pyrrolidin-1-yl)spiro[adamantan-2,2'-[1,3]oxathiole]* (**6e**). The reaction of **8c** with **1f** was complete after 3 d. The solvent was evaporated, and the crude product was purified by CC (CH_2Cl_2/petroleum ether 2:3). Compound **6e** consisted of a 61:39 mixture of two rotamers. Yield of **6e**: 171 mg (45%). Yellow viscous oil. $[\alpha]_D = -41.2$ (c = 1; CH_2Cl_2). IR (KBr): 2912*s*, 1698*s* (C=O), 1453*m*, *1394s*, 1255*w*, 1167*m*, 1000*m*, 916*w*, 904*w*, 736*m*. ^{1}H-NMR ($CDCl_3$; values for the minor rotamer in italics): 1.44 (br. *s*, 9H, *t*Bu); 1.65–2.35 (*m*, 18H, C*H*$_2$C*H*$_2$, 4 C*H*, 5 C*H*$_2$); 3.38–3.45 (*m*, 2H, C*H*$_2$N); 4.32–4.44 (*m*, 1H, CHN); 5.10, *5.20* (br. *s*, 1H, SC*H*). ^{13}C-NMR ($CDCl_3$): 23.3 (*C*H$_2$); 26.4, 26.6 (2 *C*H); 28.4 (*Me*$_3$C); 30.8 (*C*H$_2$); 33.7, 35.2, 37.4 (2:1:1, 4 *C*H$_2$); 39.4 (2 *C*H); 46.1 (*C*H$_2$N); 55.4 (*C*HN); 79.4 (Me$_3$*C*); 92.0 (S*C*H=); 107.1 (C(2')); 150.3 (C(5')); 154.2 (C=O). ESI-MS (MeOH): 416 (100, $[M+K]^+$).

4.3. N-*Boc-5'-(pyrrolidin-1-yl)spiro[2,2,4,4-tetramethyl-1-thioxocyclobutane-3,2'-[1,3]oxathiole]* (**6f**). The reaction of **8c** with 2,2,4,4-tetramethylcyclobutane-1,3-dione (**1g**) was complete after 8 h. The solvent was evaporated, and the crude product was purified by CC (CH_2Cl_2). Compound **6f** consisted of a 59:41 mixture of two rotamers. Yield of **6f**: 158 mg (41%). Pale pink crystals. M.p. 72.0-74.3° (CH_2Cl_2). $[\alpha]_D$

= –79.2 (*c* = 1; CH_2Cl_2). IR (KBr): 2968*s*, 2925*m*, 2882*w*, 1686*s* (C=O), 1459*m*, 1397*s*, 1368*m*, 1306*w*, 1165*s*, 1125*m*, 1042*s*, 1012w, 706*w*. ^{1}H-NMR ($CDCl_3$; values for the minor rotamer in italics): 1.27, 1.34, 1.35, 1.36 (4*s*, 12H, 4 Me); 1.47 (br. *s*, 9H, *t*Bu); 1.88–2.02 (*m*, 4H, C*H*$_2$C*H*$_2$); 3.38–3.45 (*m*, 2H, CH_2N); 4.41–4.52 (*m*, 1H, C*H*N); 5.15, *5.25* (br. *s*, 1H, SC*H*). ^{13}C-NMR ($CDCl_3$): 23.3 (*C*H_2); 26.7 (br. *s*, 4 Me); 28.5 (*Me*$_3$C); 30.3 (*C*H_2); 46.1 (*C*H_2N); 55.2 (*C*HN); 69.6, 70.1 (C(2'), C(4')); 79.6 (Me$_3$*C*); 91.8 (S*C*H=); 108.3 (C(2')); 150.5 (C(5')); 154.1 (C=O); 280.7 (C=S). ESI-MS (MeOH): 422 (65, [*M*+K]$^+$), 406 (100, [*M*+Na]$^+$).

Suitable crystals for the X-ray crystal-structure determination were grow from MeOH/CH_2Cl_2 in the refrigerator.

5. *X-Ray Crystal Structure Determination of* **6f** (*Table* and *Figure*)[2]). All measurements were made on an *Agilent Technologies SuperNova* area-detector diffractometer [14] using Mo$K\alpha$ radiation (λ = 0.71073 Å) from a micro-focus X-ray source and an *Oxford Instruments Cryojet XL* cooler. Data reduction was performed with *CrysAlisPro* [14]. The intensities were corrected for *Lorentz* and polarization effects, and an empirical absorption correction using spherical harmonics [14] was applied. The space group was determined by the systematic absences, packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure. Equivalent reflections, other than *Friedel* pairs, were merged. The data collection and refinement parameters are given in the *Table*. A view of the molecule is shown in the *Figure*. The structure was solved by direct methods

[2]) CCDC-1028924 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre*, *via* www.ccdc.cam.ac.uk/data_request/cif.

using *SHELXS-2013* [15], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the Me groups). The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was not applied. Refinement of the absolute structure parameter [16] yielded a value of 0.01(1), which confidently confirms that the refined model represents the true enantiomorph. Neutral atom scattering factors for non-H-atoms were taken from [17a], and the scattering factors for H-atoms were taken from [18]. Anomalous dispersion effects were included in F_c [19]; the values for f' and f'' were those of [17b]. The values of the mass attenuation coefficients are those of [17c]. The *SHELXL-2014* program [15] was used for all calculations.

Table. *Crystallographic Data for Compound* **6f**

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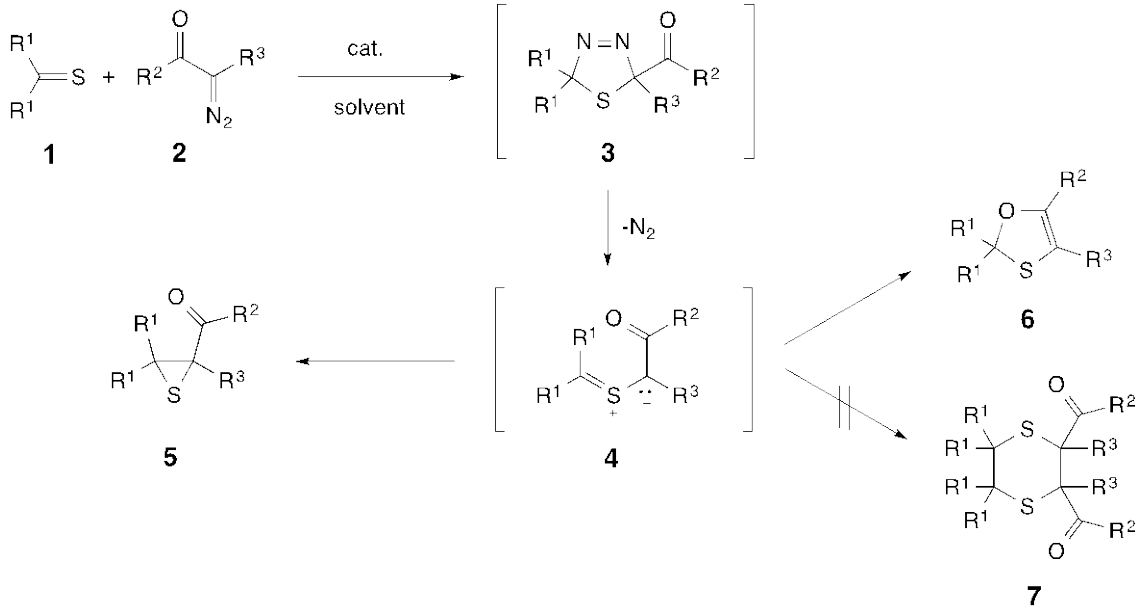
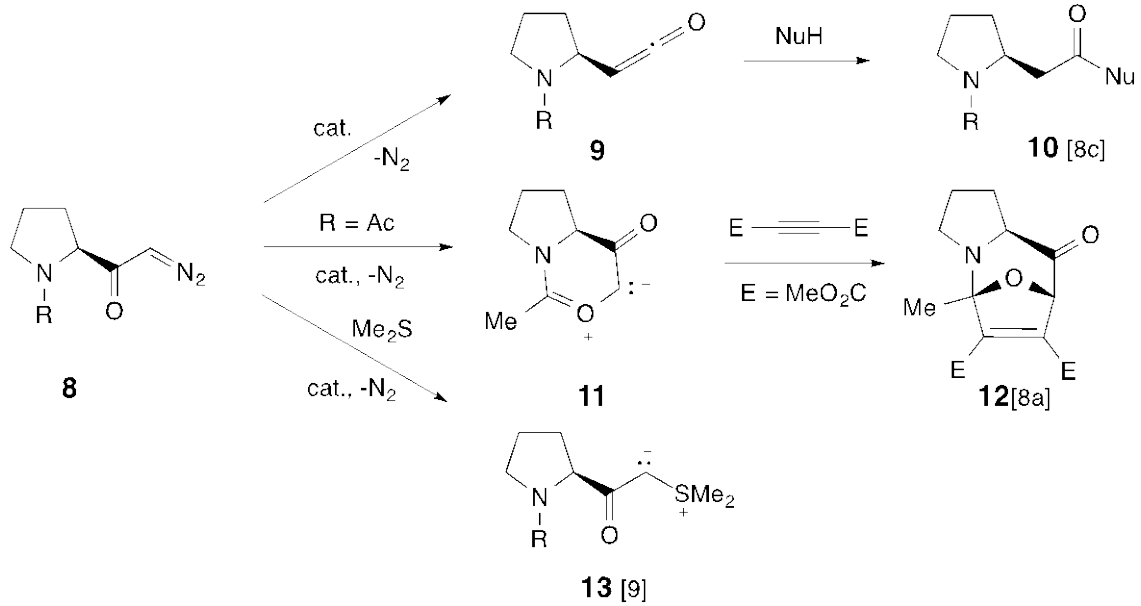
Table. *Crystallographic Data for Compound* **6f**

Crystallized from		$MeOH/CH_2Cl_2$
Empirical formula		$C_{19}H_{29}NO_3S$
Formula weight [g mol^{-1}]		383.56
Crystal color, habit		pale-pink, plate
Crystal dimensions [mm]		0.05 × 0.19 × 0.20
Temperature [K]		160(1)
Crystal system		monoclinic
Space group		$P2_1$
Z		2
Reflections for cell determination		13733
2θ range for cell determination [°]		5–57
Unit cell parameters	a [Å]	6.92133(11)
	b [Å]	9.82205(13)
	c [Å]	15.5729(2)
	β [°]	99.6213(14)
	V [$Å^3$]	1043.78(3)
D_x [g cm^{-3}]		1.220
μ(Mo$K\alpha$) [mm^{-1}]		0.272
Scan type		ω
$2\theta_{(max)}$ [°]		56.9
Transmission factors (min; max)		0.871; 1.000
Total reflections measured		20424
Symmetry independent reflections		4649
Reflections with $I > 2\sigma(I)$		4442
Reflections used in refinement		4649
Parameters refined; restraints		233; 1
Final $R(F)$ [$I > 2\sigma(I)$ reflections]		0.0261
$wR(F^2)$ (all data)		0.0641
Weights:	$w = [\sigma^2(F_o^2) + (0.0336P)^2 + 0.1546P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$	
Goodness of fit		1.041
Final Δ_{max}/σ		0.001
$\Delta\rho$ (max; min) [e $Å^{-3}$]		0.28; -0.25

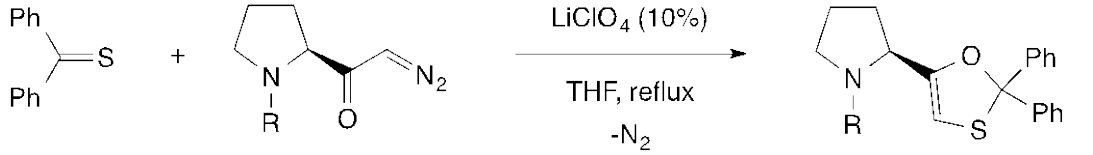
Scheme 1



Scheme 2



Scheme 3

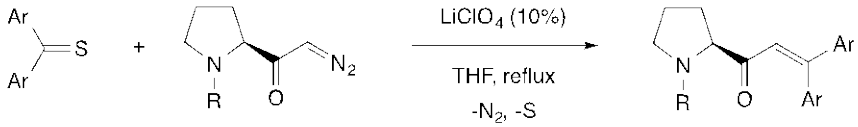


1a

8a R = PhCO (Bz)
b R = $PhCH_2$ (Bn)
c R = *t*BuOCO (Boc)

6a R = PhCO (Bz)
b R = $PhCH_2$ (Bn)
c R = *t*BuOCO (Boc)

Scheme 4

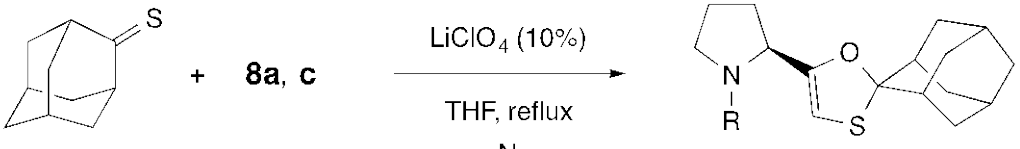


1b Ar = Thiophen-2-yl
c Ar = Selenophen-2-yl
d Ar = Furan-2-yl
e Ar, Ar = Ph, Thiophen-2-yl

8a, c

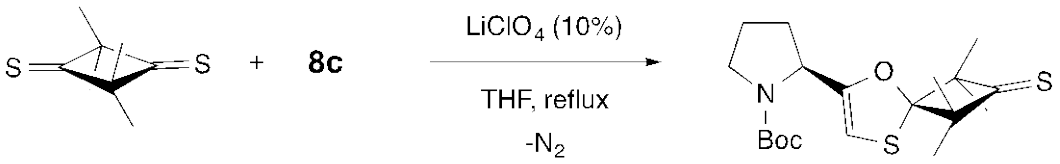
14a R = Bz, Ar = Thiophen-2-yl
b R = Bz, Ar = Selenophen-2-yl
c R = Boc, Ar = Thiophen-2-yl
d R = Boc, Ar = Selenophen-2-yl
e R = Boc, Ar = Furan-2-yl
f R = Boc, Ar, Ar = Ph, Thiophen-2-yl

Scheme 5



1f

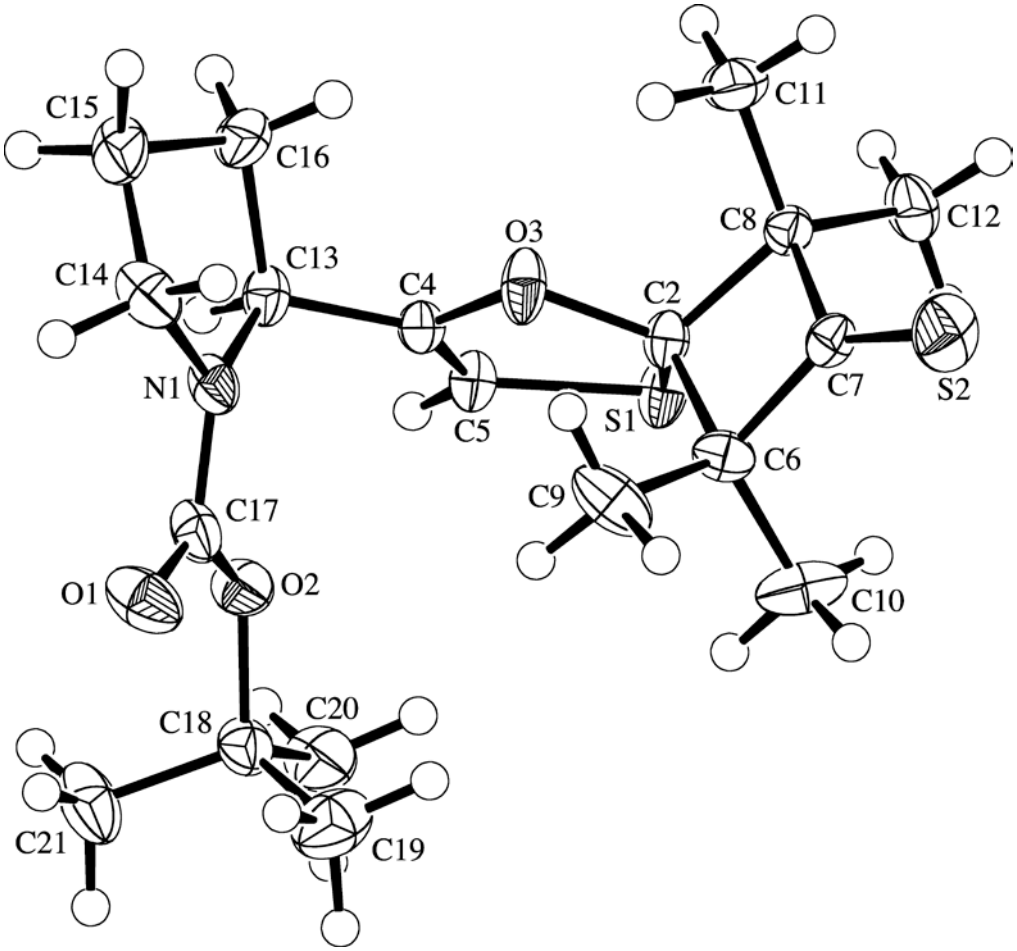
6d R = Bz
e R = Boc



1g

6f

Figure



Graphical Abstract